

Synthesis of 2-Quinuclidonium by Eliminating Water: Experimental Quantification of the High Basicity of Extremely Twisted Amides

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Materials and Methods.

Organic Synthesis

Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents passed through activated alumina columns under argon. All commercially obtained reagents were used as received. Hexamethylphosphoramide was distilled from CaH_2 and stored in a schlenk tube under argon. 3-*d*-cyclopentenoneⁱ and 6,6,7,7-tetramethyl-2-quinuclidoneⁱⁱ were prepared by known methods. Sodium azide (1- ^{15}N , 98 atom% ^{15}N) and acetic acid (1,2- $^{13}\text{C}_2$, 99 atom% ^{13}C) were purchased from Cambridge Isotope Laboratories. Lithium aluminum deuteride (98 atom% *d*) was purchased from Aldrich. Reaction temperatures were controlled using an IKAmag temperature modulator, and unless stated otherwise, reactions were performed at 23 °C. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032-0.063 mm) was used for flash column chromatography. ^1H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz), or a Varian Inova 500 (at 500 MHz), and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz), or a Varian Inova 500 (at 125 MHz), and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift, multiplicity, and coupling constant. ^2H NMR spectra were recorded on a Varian Inova 500 (at 76 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^2H NMR spectra are reported in terms of chemical shift and multiplicity. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

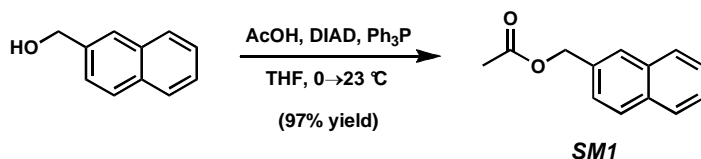
Extended Kinetic Method and Gas Phase Synthesis

All mass spectra were obtained using an LTQ linear ion trap mass spectrometer (Thermo Electron, Waltham, MA) equipped with a standard electrospray ionization source. Voltages were optimized to maximize the [**1** + H^+ + B_{ref}] dimer peak intensities for kinetic method experiments. All reference bases were purchased from Sigma-Aldrich (St. Louis, MO) and were used without further purification.

To minimize hydrolysis of **1**•HBF₄, samples containing 300 μ M of **1** and reference base were prepared with dry acetonitrile unless otherwise noted and immediately infused into the electrospray source. The noncovalently bound dimers were then isolated and subjected to CID at normalized collision energies (relative to instrument calibration and *m/z*) ranging from 18% to 85%. These percentages correspond to excitation voltage amplitudes of 0.00641V to 0.0303V for a 100 *m/z* ion. To obtain tandem MS data, 30 μ M solutions were prepared and analyzed as above under standard instrument tune conditions. Amino acid derivatives were prepared by either allowing a sample sufficient time to hydrolyze (ca. 30 minutes) or by addition of deionized water in molar excess.

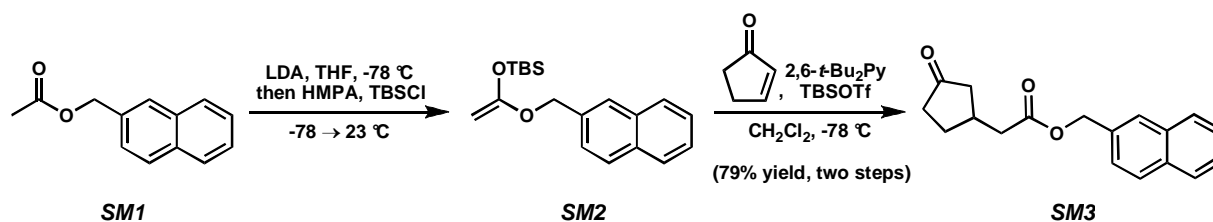
Proton affinities were calculated using hybrid density functional theory as implemented in Gaussian 03 Version 6.1 Revision D.01. Candidate structures were built using GaussView 3.0 and then submitted for optimization and vibrational frequency calculation at the B3LYP/6-311++G** level. Total energies, zero point energies (ZPE), and thermal corrections were obtained from the optimization/frequency output. Zero point corrections were scaled by an empirical factor of 0.9877 as recommended by Andersson and Uvdalⁱⁱⁱ. The basis set superposition error (BSSE) was calculated using the counterpoise (CP) method of Boys and Bernardi^{iv}.

Preparative Procedures.



Naphthalen-2-ylmethyl acetate (SM1); CAS # 35480-23-0. Ph₃P (0.787 g, 3.0 mmol, 1.5 equiv) and 2-naphthalenylmethanol (0.475 g, 3.0 mmol, 1.5 equiv) were dissolved in THF (13.4 mL, 0.15 M). Acetic acid (114 μ L, 2.0 mmol, 1.0 equiv) was added and the solution was cooled to 0 $^{\circ}$ C. DIAD (591 μ L, 3.0 mmol, 1.5 equiv) dissolved in THF (1 mL) was added dropwise over 5 min via positive pressure cannulation. After 1 h the reaction was quenched with 5 mL sat'd NaHCO₃, extracted with hexanes (3 x 20 mL), the organics were dried over MgSO₄, filtered, and concentrated under reduced pressure to an off-white solid. The crude material was purified by flash chromatography (SiO₂, 15:1 \rightarrow 9:1 Hex-Et₂O, PhMe load) to afford naphthalen-2-ylmethyl acetate (**SM1**, 0.3830 g, 1.91 mmol, 96% yield) as a white solid. *R*_f = 0.28 (9:1 Hex-Et₂O); ¹H NMR (300

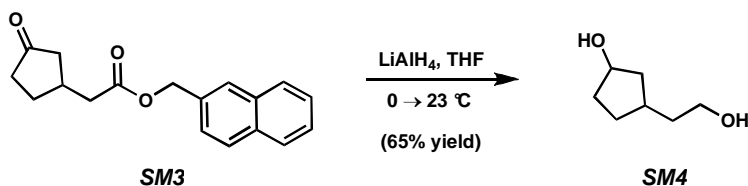
MHz, CDCl₃): δ 7.89-7.85 (comp. m, 4H), 7.53-7.47 (comp. m, 3H), 5.30 (s, 2H), 2.16 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 171.1, 133.5, 133.4, 133.3, 128.5, 128.1 (2C), 127.9, 127.5 (2C), 126.5, 126.4, 126.1, 66.6, 21.2; IR (neat film, NaCl): 3055, 2953, 1736, 1378, 1364, 1248, 1030, 951, 896, 863, 822, 744, 480 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calc'd for [C₁₃H₁₂O₂]⁺, 200.0837; found, 200.0844; mp = 53-55 °C.



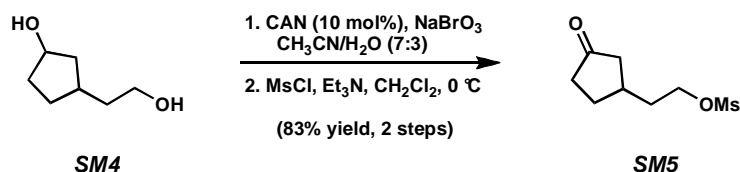
Naphthalen-2-ylmethyl 2-(3-oxocyclopentyl)ethanoate (SM3). To a cooled solution of *i*-Pr₂NH (341 μ L, 2.44 mmol, 1.15 equiv) in THF (2.12 mL, 1 M) at 0 °C was added *n*-BuLi (2.5 M in hexane) dropwise. After stirring for 15 min, the solution was cooled to -78 °C and a solution of 2-naphthylmethyl acetate (**SM1**, 424.0 mg, 2.12 mmol, 1.0 equiv) in THF (1 mL) was added dropwise via positive pressure cannulation. After 15 min, HMPA (332 μ L, 1.91 mmol, 0.9 equiv), then TBSCl (351.0 mg, 2.33 mmol, 1.1 equiv) in THF (0.80 mL) were added and the cooling bath was removed. The reaction was warmed to ambient temperature and concentrated under reduced pressure. The resulting thick oil was dissolved in 9:1 Hex-Et₂O (50 mL) and washed with distilled water (3 x 20 mL, pH ~ 7) and sat'd brine. The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting yellow oil solidified after several hours under high vacuum to afford TBS-silylenol ether **SM2** (650.9 mg) which was used without further purification in the subsequent reaction. *R_f* = unstable to SiO₂.

To a solution of **SM2** (1.2 equiv), cyclopentenone (145 μ L, 1.72 mmol, 1.0 equiv), and 2,6-di-*tert*-butylpyridine (465 μ L, 2.07 mmol, 1.2 equiv) in CH₂Cl₂ (20.7 mL, 0.1 M) cooled to -78 °C was added a solution of TBSOTf (475 μ L, 2.07 mmol, 1.2 equiv) in CH₂Cl₂ (2.1 mL) dropwise over 15 min. Following consumption of cyclopentenone by TLC (15 min), the cooling bath was removed and the reaction was quenched with 15 mL of 3% aq HCl. After stirring for 30 min the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL), the organics dried over MgSO₄, filtered, and concentrated under reduced pressure to a yellow solid. The crude product was purified by flash chromatography (SiO₂, 9:1→4:1→3:1 Hex-EtOAc, dry load) to afford naphthalen-2-ylmethyl 2-(3-oxocyclopentyl)ethanoate (**SM3**, 385.4 mg, 1.37 mmol) as a light

yellow oil. $R_f = 0.23$ (1:1 Hex-Et₂O); ¹H NMR (300 MHz, CDCl₃): δ 7.87-7.82 (comp. m, 4H), 7.53-7.49 (comp. m, 2H), 7.45 (dd, $J = 8.5, 1.9$ Hz, 1H), 5.30 (s, 2H), 2.70-2.57 (m, 1H), 2.55 (d, $J = 1.1$ Hz, 1H), 2.53 (d, $J = 2.9$ Hz, 1H), 2.51-2.45 (m, 1H), 2.38-2.11 (comp. m, 3H), 1.90 (ddd, $J = 18.1, 9.8, 1.1$ Hz, 1H), 1.66-1.51 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 218.4, 172.0, 133.3 (2C), 133.2, 128.6, 128.1, 127.9, 127.7, 126.5 (2C), 126.0, 66.7, 44.7, 39.9, 38.4, 33.6, 29.4; IR (neat film, NaCl): 3049, 2956, 1737, 1271, 116, 817 cm⁻¹; HRMS-EI (m/z): [M]⁺⁺ calc'd for [C₁₈H₁₈O₃]⁺⁺, 282.1256; found, 282.1257.

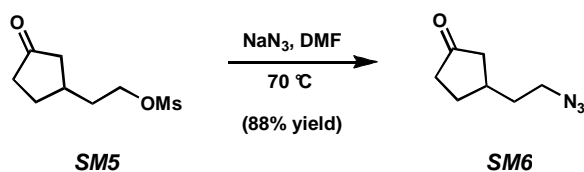


3-(2-hydroxyethyl)cyclopentanol (SM4). To a slurry of LiAlH₄ (74.3 mg, 1.96 mmol, 4.0 equiv) in THF (4.9 mL, 0.1M) at 0 °C was added ketoester **SM3** (138.1 mg, 0.498 mmol, 1.0 equiv) in 1.0 mL THF. The cooling bath was removed and the reaction was stirred for 2.5 h at ambient temperature. The reaction was then cooled to 0 °C and carefully quenched by slow addition of Na₂SO₄•10H₂O. When gas evolution had ceased, the flask was diluted up to 25 mL with EtOAc and stirred vigorously at ambient temperature for 2 h. The fine precipitate was then filtered through celite, washing with excess EtOAc, and the resulting filtrate was concentrated under reduced pressure to an off-white solid. This residue was purified by flash chromatography (SiO₂, 2:1 → 1:0 EtOAc-Hex) to afford ~1:1 mixture of diastereomers of 3-(2-hydroxyethyl)cyclopentanol (**SM4**, 42.6 mg, 0.320 mmol, 65% yield) as a colorless oil. $R_f = 0.15$ (3:1 EtOAc-Hex); ¹H NMR (500 MHz, CD₃OD): δ 4.26 (*anti* diastereomer, ddd, $J = 5.6, 5.6, 2.9, 2.9$ Hz, 0.47H), 4.21 (*syn* diastereomer, dddd, $J = 5.9, 5.9, 5.9, 5.9$ Hz, 0.53H), 3.56 (app t, $J = 6.8$ Hz, 2H), 2.20 (ddd, $J = 16.4, 7.8, 7.8$ Hz, 0.53H), 2.14 (ddd, $J = 14.2, 7.6, 7.6$ Hz, 0.53H), 1.98-1.90 (comp. m, 1.5H), 1.81-1.72 (comp. m, 1.5H), 1.65-1.60 (comp. m, 1.5H), 1.59-1.51 (comp. m, 1.5H), 1.44-1.31 (m, 1H), 1.19-1.12 (m, 1H); ¹³C NMR (125 MHz, CD₃OD): δ 74.1 (*syn*), 62.2, 62.1 (*syn*), 43.1, 42.9 (*syn*), 40.6 (*syn*), 40.1, 36.1 (*syn*), 35.8 (*syn*), 35.6, 35.2, 31.5, 31.2 (*syn*); IR (neat film, NaCl): 3323 (broad), 2931, 2864, 1434, 1344, 1052, 1013 cm⁻¹; HRMS-EI (m/z): [M]⁺⁺ calc'd for [C₇H₁₄O₂]⁺⁺, 130.0994; found 130.0994.



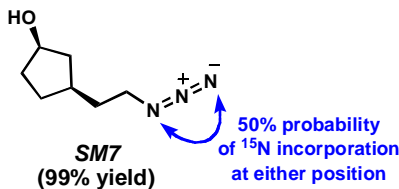
2-(3-oxocyclopentyl)ethyl methanesulfonate (SM5).^v CH₃CN (2.8 mL, 0.167 M), CAN (36.9 mg, 0.673 mmol, 0.1 equiv), NaBrO₃ (101.5 mg, 0.673 mmol, 1.0 equiv), and distilled H₂O (1.2 mL) were added to diol **SM4** (87.6 mg, 0.673 mmol, 1.0 equiv) in a vial and stirred vigorously. Following consumption of diol **SM4** by TLC (ca. 6 h), the reaction was concentrated under reduced pressure. The resulting slurry was taken up in 10 mL H₂O, extracted with EtOAc (3 x 25 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford a crude yellow oil (85.5 mg).

The resulting crude material was dissolved in CH₂Cl₂ (1.35 mL, 0.5 M), cooled to 0 °C, and MsCl (77.4 μL, 1.0 mmol, 1.5 equiv) and Et₃N (167 μL, 1.2 mmol, 1.8 equiv) were added sequentially. After 5 min, the reaction was quenched with sat'd aq. NaHCO₃ (1 mL) and diluted up to 10 mL with CH₂Cl₂. The biphasic solution was further diluted with sat'd NaHCO₃ (2 mL) and sat'd brine (2 mL), the layers were separated, and the aqueous was extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were dried over MgSO₄, filtered, and concentrated to a light yellow solid under reduced pressure. This residue was purified by flash chromatography (SiO₂, 2:1 → 1:2 Hex-EtOAc, dry load) to afford 2-(3-oxocyclopentyl)ethyl methanesulfonate (**SM5**, 115.4 mg, 0.560 mmol, 83% yield over two steps) as a colorless oil. *R*_f = 0.31 (3:1 EtOAc-Hex); ¹H NMR (300 MHz, CDCl₃): δ 4.29 (app dt, *J* = 6.4, 2.4, 2.4 Hz, 2H), 3.02 (s, 3H), 2.51-2.42 (m, 1H), 2.40-2.12 (comp. m, 4H), 1.95-1.89 (comp. m, 2H), 1.84 (ddd, *J* = 17.6, 7.7, 1.3 Hz, 1H), 1.64-1.48 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 218.3, 68.2, 44.8, 38.5, 37.6, 35.0, 33.8, 29.4; IR (neat film, NaCl): 3023, 2935, 1737, 1350, 1173, 954 cm⁻¹; HRMS-EI (*m/z*): [*M*]⁺ calc'd for [C₈H₁₄O₄S]⁺, 206.0613; found 206.0622.

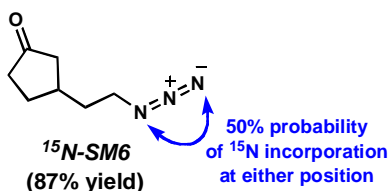


3-(2-azidoethyl)cyclopentanone (SM6). To a solution of mesylate **SM5** (50.2 mg, 0.243 mmol, 1.0 equiv) in DMF (0.50 mL, 0.5 M) was added NaN₃ (17.4 mg, 0.268 mmol, 1.1 equiv), and

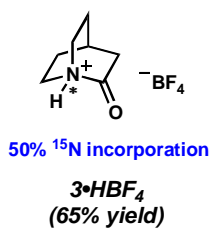
the mixture was warmed to 70 °C until consumption of **SM5** by TLC. The reaction was cooled to 0 °C and stirred for 15 min, followed by dilution with Et₂O. The suspension was filtered through a plug of celite with Et₂O, concentrated under reduced pressure, and purified by flash chromatography (SiO₂, 6:1 → 3:1 Hex-Et₂O, PhMe load) to afford 3-(2-azidoethyl)cyclopentanone (**SM6**, 32.8 mg, 0.214 mmol, 88% yield) as a colorless oil. R_f = 0.25 (3:1 Hex-EtOAc); characterization data for this compound have previously been reported.^{vi}



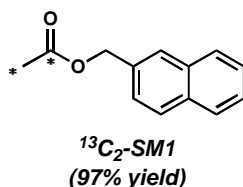
(¹⁵N)-3-(2-azidoethyl)cyclopentanol (**SM7**).^{vi} Prepared by a known method using (1-¹⁵N)-NaN₃. The reaction was purified by flash chromatography (SiO₂, 3:1 → 1:1 Hex-Et₂O, PhMe load) to afford ¹⁵N-labeled azidoalcohol **SM7** (186.1 mg, 1.19 mmol, 99% yield) as colorless oil. R_f = 0.14 (1:1 Hex-Et₂O); IR (neat film, NaCl): 3344, 2946, 2868, 2074, 1339, 1243 cm⁻¹; HRMS-FAB (m/z): [M+H]⁺ calc'd for [C₇H₁₄N₂O¹⁵N]⁺, 157.1107; found 157.1141. All other characterization data are identical to that reported.



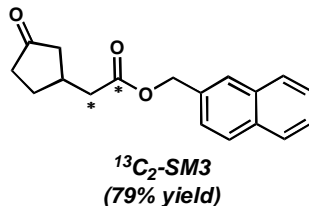
(¹⁵N)-3-(2-azidoethyl)cyclopentanone (¹⁵N-SM6).^{vi} Prepared by a known method. The reaction was purified by flash chromatography (SiO₂, 6:1 → 3:1 Hex-Et₂O) to afford ketoazide ¹⁵N-SM6 (155.5 mg, 1.00 mmol, 87% yield) as colorless oil. R_f = 0.26 (1:1 Hex-Et₂O); IR (neat film, NaCl): 2931, 2873, 2076, 1740, 1242, 1160 cm⁻¹. All other characterization data are identical to that reported.



1-¹⁵N-2-quinuclidonium tetrafluoroborate (3•HBF₄).^{vi} Prepared by a known method. The crude reaction precipitate was transferred to a glovebox and recrystallized 2X by slow diffusion of Et₂O into CH₃CN at -20 °C to afford **3•HBF₄** (127.7 mg, 0.598 mmol, 65% yield) as white needles. HRMS-FAB (*m/z*): [M+H]⁺ calc'd for [C₇H₁₂O¹⁵N]⁺, 127.0889; observed 127.0855; [M+H]⁺ calc'd for [C₇H₁₂NO]⁺, 126.0919; observed 126.0915; relative peak ratio = 1:1.

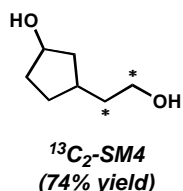


Naphthalen-2-ylmethyl (¹³C₂)-acetate (¹³C₂-SM1): Prepared as above to afford **¹³C₂-SM1** (0.8326 g, 4.12 mmol, 97% yield) as an off-white solid. ¹H NMR (300 MHz, CDCl₃): δ 7.87-7.83 (comp. m, 4H), 7.53-7.45 (comp. m, 3H), 5.27 (d, *J*_{H-13C} = 3.2 Hz, 2H), 2.13 (dd, *J*_{H-13C} = 129.7, 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃): δ 170.9 (d, *J*_{13C-13C} = 59.4 Hz), 21.1 (d, *J*_{13C-13C} = 59.2 Hz); IR (neat film, NaCl): 3054, 2955, 1693, 1360, 1276, 1218, 1024, 970, 951, 897, 864, 823, 744 cm⁻¹; HRMS-EI (*m/z*): [M]⁺ calc'd for [C₁₁H₁₂O₂¹³C₂]⁺, 202.0904; found 202.0913; mp = 54-56 °C.

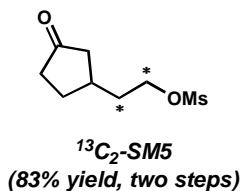


Naphthalen-2-ylmethyl 2-(3-oxocyclopentyl)-¹³C₂-ethanoate (¹³C₂-SM3). Prepared as above to afford **¹³C₂-SM3** (0.4204 g, 1.42 mmol, 79% yield) as a light yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 7.87-7.82 (comp. m, 4H), 7.53-7.49 (comp. m, 2H), 7.45 (dd, *J* = 8.5, 1.6 Hz, 1H), 5.30 (d, *J* = 3.2 Hz, 2H), 2.54 (dddd, *J*_{H-13C} = 129.2, 6.9 Hz, *J* = 10.9, 2.0 Hz, 2H), 2.71-2.58 (m,

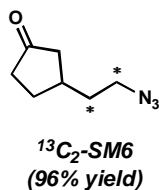
1H), 2.49 (ddd, $J = 16.8, 7.4$ Hz, $J_{H-13C} = 1.3$ Hz, 1H), 2.28-2.11 (comp. m, 3H), 1.96 (dddd, $J = 18.1, 10.4, 5.3$ Hz, $J_{H-13C} = 1.3$ Hz, 1H), 1.67-1.50 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 172.0 (d, $J_{13C-13C} = 57.2$ Hz), 39.9 (d, $J_{13C-13C} = 57.5$ Hz); IR (neat film, NaCl): 3054, 2958, 1740, 1690, 1403, 1150, 1124, 818, 754 cm^{-1} ; HRMS-EI (m/z): $[\text{M}]^{++}$ calc'd for $[\text{C}_{16}\text{H}_{18}\text{O}_3^{13}\text{C}_2]^{++}$, 284.1323; found 284.1322. All other characterization data are identical to above.



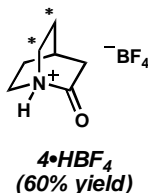
3-(2- $^{13}\text{C}_2$ -hydroxyethyl)cyclopentanol ($^{13}\text{C}_2\text{-SM4}$). Prepared as above to afford ~1:1 mixture of diastereomers of $^{13}\text{C}_2\text{-SM4}$ (54.9 mg, 0.415 mmol, 74% yield) as a colorless oil. ^1H NMR (300 MHz, CD_3OD): δ 4.26 (dddd, $J = 5.6, 5.6, 2.9, 2.9$ Hz, 0.44H), 4.21 (dddd, $J = 4.8, 4.8, 4.8, 4.8, 0.56$ H), 3.56 (dddd, $J_{H-13C} = 140.2, 6.9$ Hz, $J = 6.9, 2.4$ Hz, 2H), 2.18-2.09 (m, 1H), 2.0-1.7 (comp. m, 3H), 1.65-1.49 (m, 1H), 1.46-1.28 (comp. m, 2H), 1.23-1.09 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 62.2 (d, $J_{13C-13C} = 37.3$ Hz, 0.44C), 62.1 (d, $J_{13C-13C} = 37.3$ Hz, 0.56C), 40.6 (d, $J_{13C-13C} = 37.3$ Hz, 0.56C), 40.1 (d, $J_{13C-13C} = 37.3$ Hz, 0.44C). All other characterization data are identical to above.



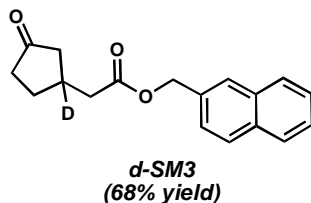
2-(3-oxocyclopentyl)($^{13}\text{C}_2$)-ethyl methanesulfonate ($^{13}\text{C}_2\text{-SM5}$). Prepared as above to afford $^{13}\text{C}_2\text{-SM5}$ (71.7 mg, 0.344 mmol, 83% yield over two steps) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 4.30 (dddd, $J_{H-13C} = 149.4, 6.4$ Hz, $J = 6.4, 2.7$ Hz, 2H), 3.03 (s, 3H), 2.47 (ddd, $J = 17.8, 7.5$ Hz, $J_{H-13C} = 1.0$ Hz, 1H), 2.41-2.08 (comp. m, 5H), 1.85 (dddd, $J = 17.8, 10.1, 5.1$ Hz, $J_{H-13C} = 1$ Hz, 1H), 1.74-1.66 (m, 1H), 1.63-1.52 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 68.1 (d, $J_{13C-13C} = 37.9$ Hz), 35.0 (d, $J_{13C-13C} = 38.2$ Hz); HRMS-EI (m/z): $[\text{M}]^{++}$ calc'd for $[\text{C}_6\text{H}_{14}\text{SO}_4^{13}\text{C}_2]^{++}$, 208.0680; found 208.0688. All other characterization data are identical to above.



3-(2-azidoethyl)(¹³C₂)-cyclopentanone (¹³C₂-SM6). Prepared as above to afford ¹³C₂-SM6 (28.5 mg, 0.184 mmol, 96% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 3.36 (app ddt, *J*_{H-13C} = 141.4, 6.9 Hz, *J* = 3.2 Hz, 2H), 2.44 (dd, *J* = 17.8, 8.0 Hz, 1H), 2.37-2.11 (comp. m, 4H), 2.00-1.91 (m, 1H), 1.83 (ddd, *J* = 17.6, 9.8, 4.8 Hz, 1H), 1.62-1.49 (comp. m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 50.0 (d, *J*_{13C-13C} = 36.8 Hz), 34.6 (d, *J*_{13C-13C} = 36.8 Hz). All other characterization data are identical to above.

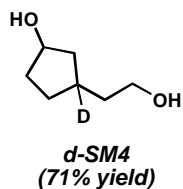


5,6-¹³C₂-2-quinuclidonium tetrafluoroborate (4•HBF₄). Prepared as above to afford 4•HBF₄ (36.5 mg, 0.170 mmol, 60% yield) as white needles. ¹H NMR (300 MHz, CD₃CN): δ 7.99 (br s, 1H), 3.69 (m, 2H), 3.69 (m, *J*_{H-13C} = 150.4 Hz, 2H), 2.97 (app. d, *J* = 5.4, 3.3 Hz, 3H), 2.55-2.47 (m, 1H), 1.98 (m, 2H), 1.98 (m, *J*_{H-13C} = 135.4 Hz, 2H); ¹³C NMR (75 MHz, CD₃CN): δ 47.9 (d, *J*_{13C-13C} = 32.6 Hz), 22.6 (d, *J*_{13C-13C} = 32.6 Hz); HRMS-FAB (*m/z*): [M+H]⁺ calc'd for [C₅H₁₂NO¹³C₂]⁺, 128.0986; observed 128.0960.

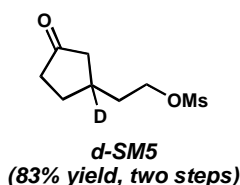


Naphthalen-2-ylmethyl 2-(3-oxocyclopentyl)-d-ethanoate (d-SM3). Prepared as above to afford d-SM3 (0.3283 g, 1.15 mmol, 68% yield) as a light yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 7.87-7.82 (comp. m, 4H), 7.53-7.49 (comp. m, 2H), 7.45 (dd, *J* = 8.5, 1.6 Hz, 1H), 5.30 (s, 2H), 2.53 (dd, *J* = 16.6, 16.6 Hz, 2H), 2.48 (d, *J* = 18.6 Hz, 1H), 2.37-2.11 (comp. m, 3H), 1.89 (d, *J* =

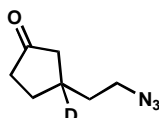
18.6 Hz, 1H), 1.64-1.51 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 218.4, 172.0, 133.3 (2C), 128.6, 128.1, 127.9, 127.6, 126.5 (2C), 126.0, 66.7, 44.6, 39.7, 38.4, 33.2 (t, $J_{\text{CD}} = 20.2$ Hz), 29.2; ^2H NMR (76 MHz, CHCl_3): δ 2.66 (s); HRMS-EI (m/z): $[\text{M}]^{+\bullet}$ calc'd for $[\text{C}_{18}\text{H}_{17}\text{O}_3^2\text{H}]^{+\bullet}$, 283.1319; found 283.1323. All other characterization data are identical to above.



3-*d*-(2-hydroxyethyl)cyclopentanol (*d*-SM4). Prepared as above to afford ~1:1 mixture of diastereomers of ***d*-SM4** (46.0 mg, 0.351 mmol, 71% yield) as a colorless oil. ^1H NMR (300 MHz, CD_3OD): δ 4.26 (ddd, $J = 8.2, 3.5, 2.4$ Hz, 0.45H), 4.21 (ddd, $J = 11.3, 6.4, 6.4$ Hz, 0.55H), 3.56 (app t, $J = 6.9$ Hz, 2H), 2.13 (dd, $J = 13.3, 6.4$ Hz, 0.45H), 1.99-1.88 (m, 0.55H), 1.82-1.70 (comp. m, 2H), 1.59 (dt, $J = 22.3, 6.9$, 3H), 1.44-1.30 (m, 1H), 1.14 (dd, $J = 12.0, 4.5$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ 74.1, 62.2, 62.1, 43.0, 42.7, 40.5, 40.0, 35.8, 35.6, 35.6 (t, $J_{\text{CD}} = 19.5$ Hz), 34.8 (t, $J_{\text{CD}} = 19.5$ Hz), 31.4, 31.1; ^2H NMR (76 MHz, CH_3OH): δ 2.14 (s), 1.87 (s). All other characterization data are identical to above.

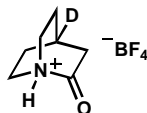


2-*d*-(3-oxocyclopentyl)-ethyl methanesulfonate (*d*-SM5). Prepared as above to afford ***d*-SM5** (60.3 mg, 0.291 mmol, 83% yield over two steps) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 4.30 (app dt, $J = 6.1, 2.7$ Hz, 2H), 3.03 (s, 3H), 2.46 (d, $J = 18.1$ Hz, 1H), 2.40-2.12 (comp. m, 3H), 1.91 (app t, $J = 6.4$ Hz, 2H), 1.85 (d, $J = 18.6$ Hz, 1H), 1.61-1.50 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 218.3, 68.1, 44.7, 38.5, 37.7, 34.9, 33.4 (t, $J_{\text{CD}} = 19.8$ Hz), 29.3; ^2H NMR (76 MHz, CHCl_3): δ 2.35 (s); HRMS-EI (m/z): $[\text{M}]^{+\bullet}$ calc'd for $[\text{C}_8\text{H}_{13}\text{O}_4\text{S}^2\text{H}]^{+\bullet}$, 207.0676; found 207.0673. All other characterization data are identical to above.



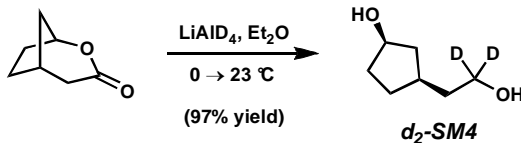
***d*-SM6**
(88% yield)

3-*d*-(2-azidoethyl)cyclopentanone (*d*-SM6). Prepared as above to afford ***d*-SM6** (39.3 mg, 0.255 mmol, 88% yield) as a colorless oil. ^1H NMR (300 MHz, CDCl_3): δ 3.36 (ddd, $J = 6.8, 6.8, 2.9$ Hz, 2H), 2.43 (d, $J = 18.3$ Hz, 1H), 2.36-2.30 (m, 1H), 2.23-2.14 (comp. m, 2H), 1.83 (d, $J = 18.1$ Hz, 1H), 1.755 (ddd, $J = 6.8, 6.8, 3.7$ Hz, 2H), 1.58-1.51 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 218.6, 50.0, 44.8, 38.5, 34.6, 34.3 (t, $J_{\text{CD}} = 19.8$ Hz), 29.4; ^2H NMR (76 MHz, CHCl_3): δ 2.29 (s);. All other characterization data are identical to above.



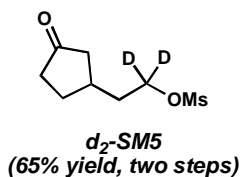
5•HBF₄
(67% yield)

4-*d*-2-quinuclidonium tetrafluoroborate (5•HBF₄). Prepared as above to afford **5•HBF₄** (33.0 mg, 0.154 mmol, 67% yield) as white needles. ^1H NMR (300 MHz, CD_3CN): δ 7.95 (br s, 1H), 3.78-3.58 (m, 4H), 2.96 (s, 2H), 2.00-1.95 (m, 4H); ^2H NMR (76 MHz, CH_3CN): δ 2.49 (s); HRMS-FAB (m/z): $[\text{M}+\text{H}]^+$ calc'd for $[\text{C}_7\text{H}_{11}\text{NO}^2\text{H}]^+$, 127.0982; observed 127.0943.

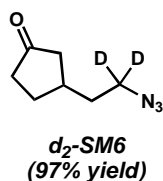


3-(2-*d*₂-hydroxyethyl)cyclopentanol (*d*₂-SM4).^{vi} Prepared by a known method using LiAlD_4 . Diol ***d*₂-SM4** isolated as a colorless oil (0.6317 g, 4.78 mmol, 97% yield) with >98% *d*-incorporation. ^1H NMR (300 MHz, CDCl_3): δ 4.21 (dddd, $J = 5.8, 5.8, 5.8, 5.8$ Hz, 1H), 2.14 (ddd, $J = 13.6, 7.2, 7.2$ Hz, 1H), 2.01-1.85 (m, 1H), 1.83-1.70 (comp. m, 2H), 1.64-1.55 (comp. m, 3H), 1.48-1.31 (m, 1H), 1.15 (dddd, $J = 14.4, 9.6, 5.6, 0.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ 74.1, 61.4, 42.9, 40.4, 36.0, 35.8, 31.2; ^2H NMR (76 MHz, CH_3OH): δ 3.51 (s); HRMS-EI (m/z): $[\text{M}]^{+*}$

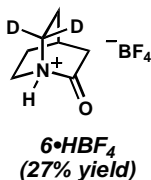
calc'd for $[\text{C}_7\text{H}_{12}\text{O}_2^2\text{H}_2]^+$, 132.1119; found 132.1113. All other characterization data are identical to above.



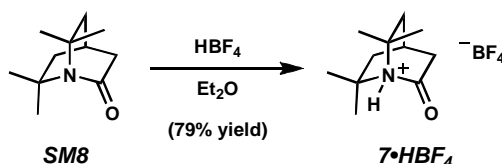
2-(3-oxocyclopentyl)-*d*₂-ethyl methanesulfonate (*d*₂-SM5). Prepared as above to afford ***d*₂-SM5** (0.3775 g, 1.81 mmol, 65% yield over two steps) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 3.01 (s, 3H), 2.49-2.40 (m, 1H), 2.39-2.10 (comp. m, 4H), 1.89 (d, *J* = 6.9 Hz, 2H), 1.83 (ddd, *J* = 17.5, 7.4, 1.3 Hz, 1H), 1.63-1.47 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 218.3, 67.6 (pentet, *J*_{CD} = 22.7 Hz), 44.8, 38.4, 37.6, 34.7, 33.7, 29.4; ²H NMR (76 MHz, CHCl₃): δ 4.29 (s); HRMS-EI (*m/z*): [*M*]⁺ calc'd for $[\text{C}_8\text{H}_{12}\text{SO}_4^2\text{H}_2]^+$, 208.0738; found 208.0741. All other characterization data are identical to above.



3-(2-*d*₂-azidoethyl)cyclopentanone (*d*₂-SM6). Prepared as above to afford ***d*₂-SM6** (143.6 mg, 0.925 mmol, 97% yield) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ 2.48-2.39 (m, 1H), 2.37-2.11 (comp. m, 4H), 1.83 (ddd, *J* = 17.6, 9.8, 1.3 Hz, 1H), 1.74 (d, *J* = 6.7 Hz, 2H), 1.61-1.50 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 218.6, 49.3 (pentet, *J*_{CD} = 21.7 Hz), 44.8, 38.5, 34.6, 34.4, 29.4; ²H NMR (76 MHz, CHCl₃): δ 3.32 (s). All other characterization data are identical to above.



6,6-*d*₂-2-quinuclidonium tetrafluoroborate (6•HBF₄). Prepared as above to afford **XX•BF₄** (15.3 mg, 0.0712 mmol, 27% yield) as white needles. ¹H NMR (300 MHz, CD₃CN): δ 7.96 (br s, 1H), 3.77-3.58 (m, 2H), 2.97 (d, *J* = 3.2 Hz, 2H), 2.51 (app. pentet, *J* = 3.2 Hz, 1H), 2.15 (m, 2H), 2.02-1.94 (m, 2H); ²H NMR (76 MHz, CH₃CN): δ 3.68 (s), 3.59 (s); HRMS-FAB (*m/z*): [M+H]⁺ calc'd for [C₇H₁₀NO²H₂]⁺, 128.1044; observed 128.1042.



6,6,7,7-tetramethyl-2-quinuclidonium tetrafluoroborate (7•HBF₄). 6,6,7,7-tetramethyl-2-quinuclidone (**SM8**, 24.9 mg, 0.137 mmol, 1.0 equiv) was dissolved in Et₂O (1.0 mL, 0.14 M) and HBF₄ in Et₂O (54 wt% solution, 38 μL, 0.274 mmol, 2.0 equiv) was added in one portion. The reaction was stirred for 30 min and the precipitate was collected by filtration and dried under vacuum to afford **7•HBF₄** (31.6 mg, 0.117 mmol, 86% yield) as a tan solid. HRMS-FAB (*m/z*): [M+H]⁺ calc'd for [C₁₁H₂₀NO]⁺, 182.1545; observed 182.1552.

Computational Results*Table 1. Summary of Calculated Energies and Corrections*

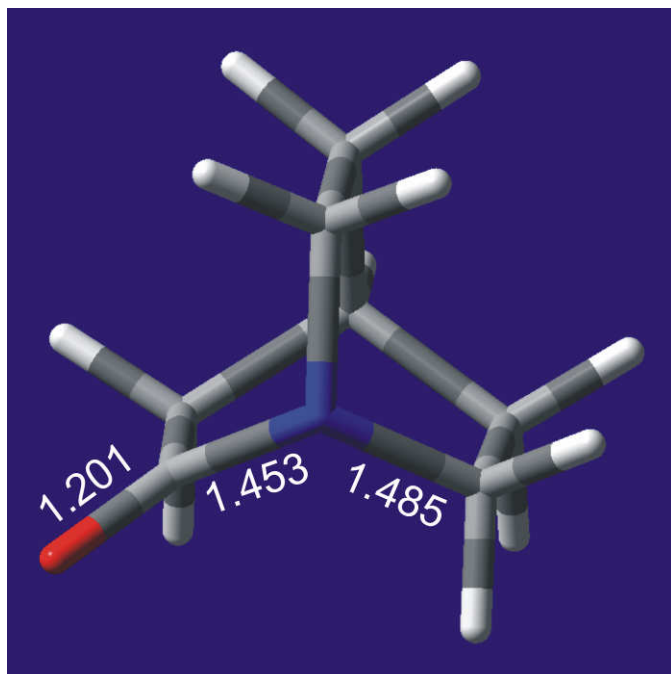
Molecule	Electronic Energy	Scaled zpe/thermal corr.	BSSE
	<i>Hartrees</i>		
1	-403.438205	0.179704	
1 + H ⁺ (N-protonated)	-403.813593	0.194329	0.001093
1 + H ⁺ (O-protonated)	-403.775347	0.191370	0.000383
7	-560.727058	0.294566	
7 + H ⁺ (N-protonated)	-561.116387	0.308837	0.001042

Table 2. Summary of Calculated Proton Affinities including ZPE, Thermal, and BSSE Corrections

	1 (N-protonation)	1 (O-protonation)	7 (N-protonation)
PA (kJ/mol)	944.3	853.5	982.0

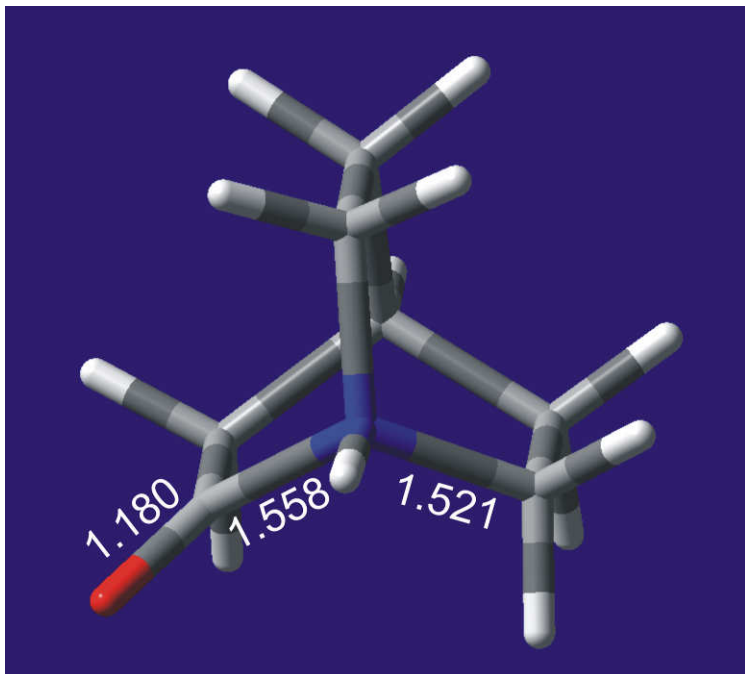
Optimized structures. Bond lengths below are given in angstroms.

Optimized Structure of 2-quinuclidone



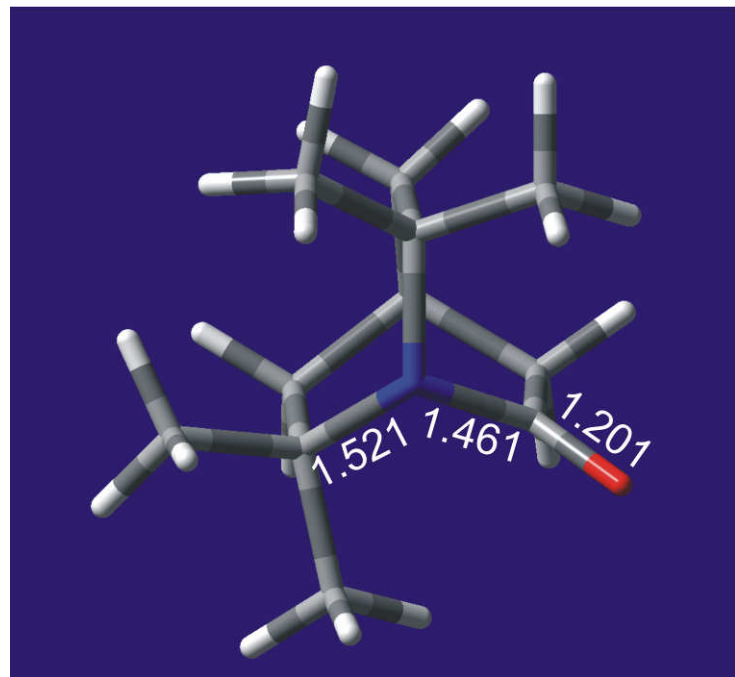
O=C-N-C dihedral angles: $\pm 121^\circ$

Optimized Structure of protonated 2-quinuclidone.



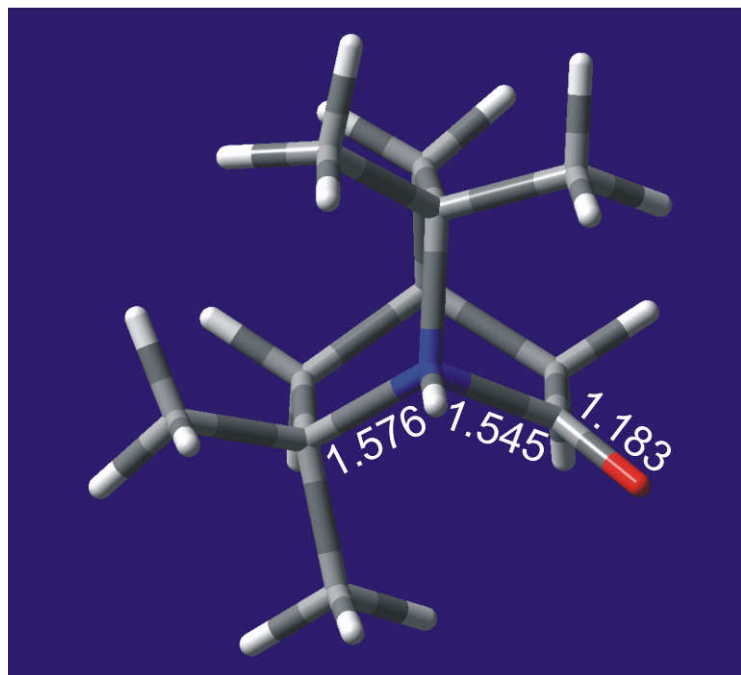
O=C-N-C dihedral angles $\pm 119^\circ$, -0.0°

Optimized Structure of Tetramethyl 2-quinuclidone.



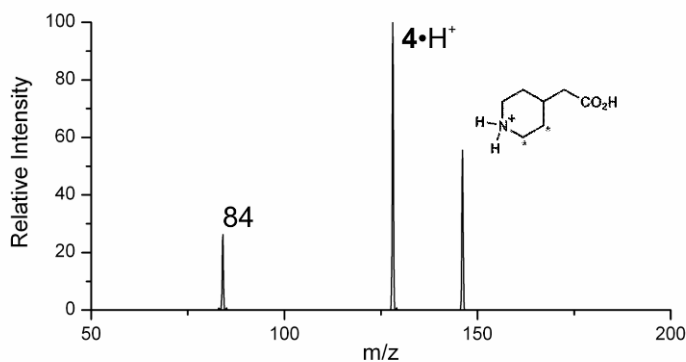
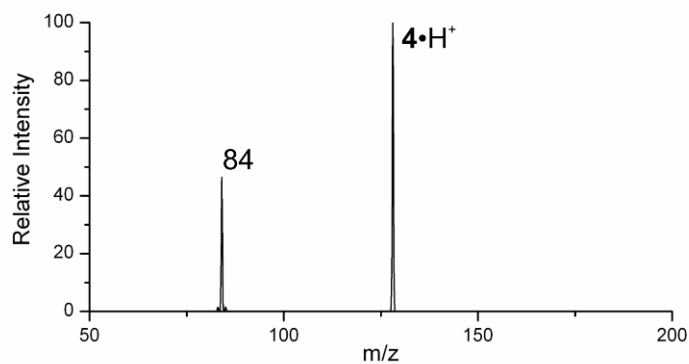
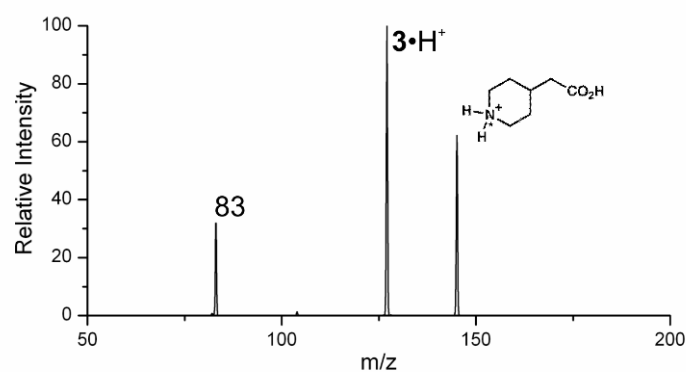
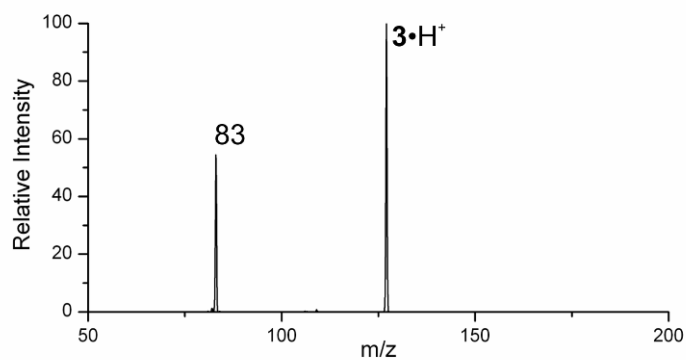
O=C-N-C dihedral angles: $\pm 118^\circ$

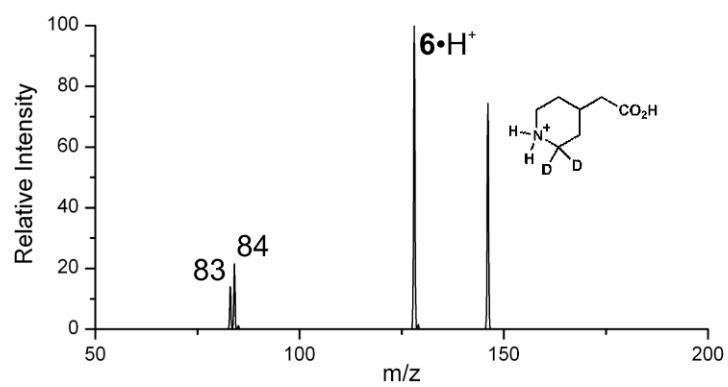
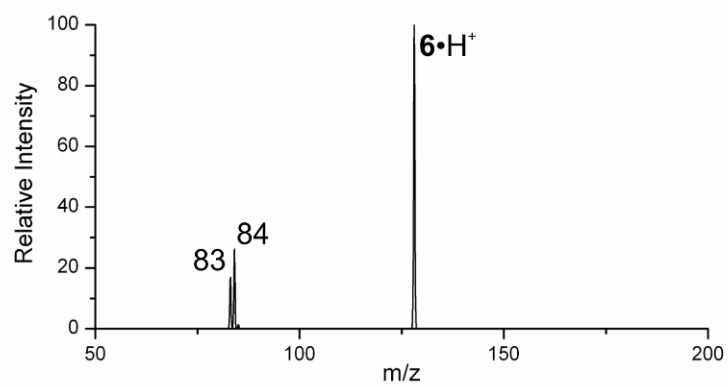
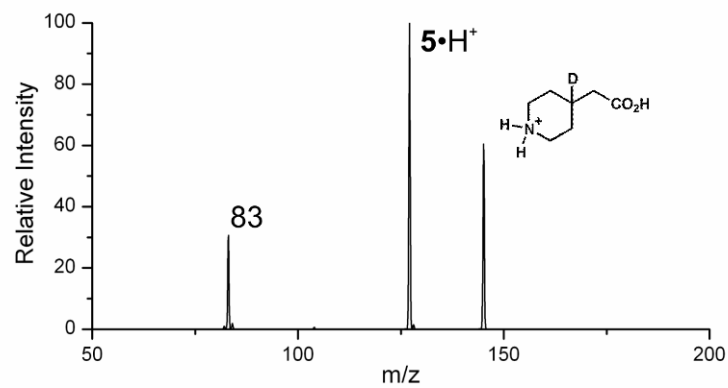
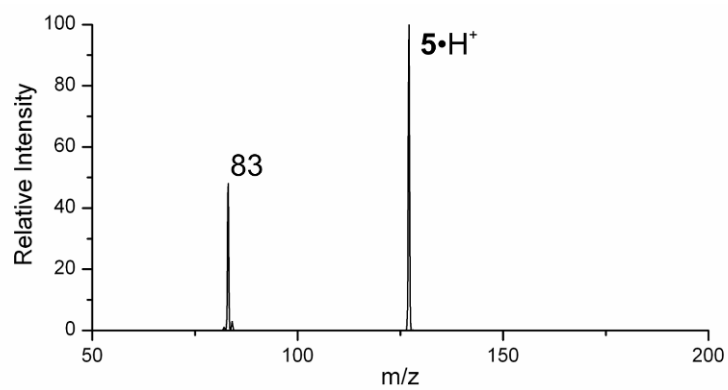
Optimized Structure of Protonated Tetramethyl 2-quinuclidone.



O=C-N-C dihedral angles: $\pm 116^\circ$, 0.0°

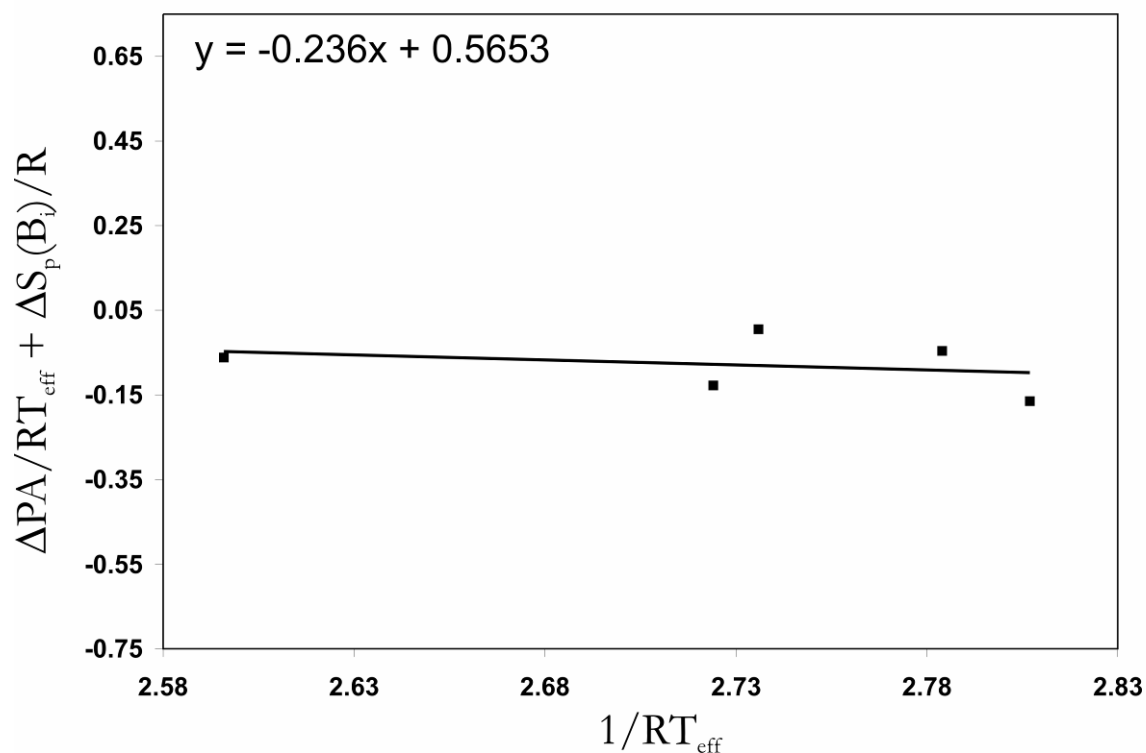
MS² spectra of 3, 4, 5, 6 and their hydrolysis products. Fragmentation patterns of isotopically labeled compounds are in agreement with mechanism proposed in Scheme 1.



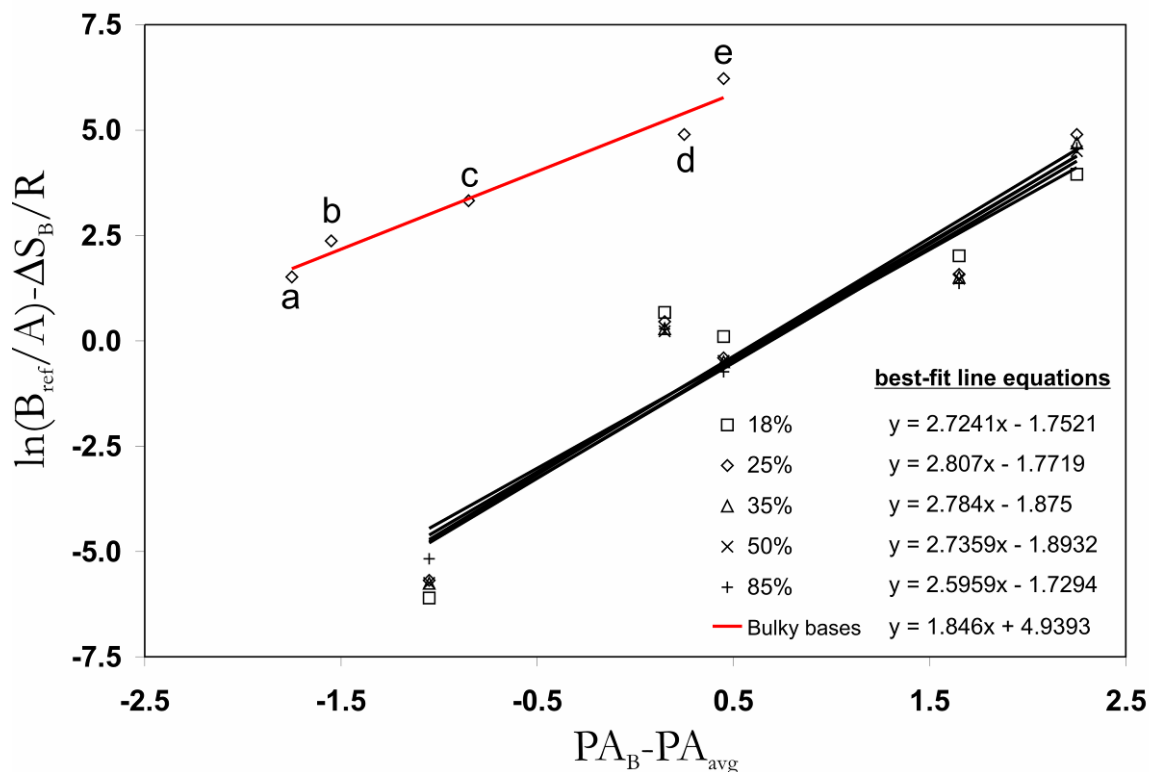


Extended Kinetic Method Plots

Second extended kinetic plot with direct entropy correction. The best-fit y-intercepts from the first entropy corrected kinetic plot shown in Figure 1 were plotted against the corresponding slopes at 18%, 25%, 35%, 50%, and 85% normalized collision energies. The slope of the line shown below is equal to $[PA_{\text{quin}} - PA_{\text{avg}}]$.



Entropy corrected kinetic plot of bulky bases. The second trend observed is associated with the proton affinity of the carbonyl oxygen of 2-quinuclidone. Bulky bases **a-e**: 3-aminopyridine; 3,5-lutidine; diisobutylamine; 2,4-lutidine; 1,4-diazabicyclo[2.2.2]-octane.



ⁱ (a) Gannon, W. F.; House, H. O. *Org. Synth.* **1973**, CV 5, 294-196. (b) Dauphin, G.; Gramain, J.-C.; Kergomard, A.; Renard, M. F.; Veschambre, H. *J. Chem. Soc., Chem. Commun.* **1980**, 318-319.

ⁱⁱ Greenburg, A.; Wu, G.; Tsai, J.-C.; Chiu, Y.-Y. *Struct. Chem.* **1993**, 4, 127-129.

ⁱⁱⁱ Andersson, M. P.; Uvdal, P. *J. Phys. Chem. A* **2005**, 109, 2937-2941.

^{iv} Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, 19, 553-566.

^v (a) Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, 23, 539-542. (b) Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1986**, 59, 105-108.

^{vi} Tani, K.; Stoltz, B. M. *Nature* **2006**, 441, 731-734 (supporting information).